



The Important Roles of Steroid Sulfatase and Sulfotransferases in Gynecological Diseases

Tea Lanišnik Rižner*

Faculty of Medicine, Institute of Biochemistry, University of Ljubljana, Ljubljana, Slovenia

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*Correspondence:

Tea Lanišnik Rižner
tea.lanisnik-rizner@mf.uni-lj.si

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Gynecological diseases such as endometriosis, adenomyosis and uterine fibroids, and gynecological cancers including endometrial cancer and ovarian cancer, affect a large proportion of women. These diseases are estrogen dependent, and their progression often depends on local estrogen formation. In peripheral tissues, estrogens can be formed from the inactive precursors dehydroepiandrosterone sulfate and estrone sulfate. Sulfatase and sulfotransferases have pivotal roles in these processes, where sulfatase hydrolyzes estrone sulfate to estrone, and dehydroepiandrosterone sulfate to dehydroepiandrosterone, and sulfotransferases catalyze the reverse reactions. Further activation of estrone to the most potent estrogen, estradiol, is catalyzed by 17-ketosteroid reductases, while estradiol can also be formed from dehydroepiandrosterone by the sequential actions of 3 β -hydroxysteroid dehydrogenase- Δ^4 -isomerase, aromatase, and 17-ketosteroid reductase. This review introduces the sulfatase and sulfotransferase enzymes, in terms of their structures and reaction mechanisms, and the regulation and different transcripts of their genes, together with the importance of their currently known single nucleotide polymorphisms. Data on expression of sulfatase and sulfotransferases in gynecological diseases are also reviewed. There are often unchanged mRNA and protein levels in diseased tissue, with higher sulfatase activities in cancerous endometrium, ovarian cancer cell lines, and adenomyosis. This can be indicative of a disturbed balance between the sulfatase and sulfotransferases enzymes, defining the potential for sulfatase as a drug target for treatment of gynecological diseases. Finally, clinical trials with sulfatase inhibitors are discussed, where two inhibitors have already concluded phase II trials, although so far with no convincing clinical outcomes for patients with endometrial cancer and endometriosis.

Keywords: endometrial cancer, endometriosis, adenomyosis, uterine fibroids, estrogen formation, estrone sulfate, dehydroepiandrosterone sulfate

STEROID SULFATASE

The formation and hydrolysis of steroid sulfates by the steroid sulfotransferase (SULT) and steroid sulfatase (STS) enzymes, respectively, represent important mechanisms in the regulation of the biological activities of many steroid hormones (Purohit et al., 1998). STS (E.C. 3.1.6.2.) hydrolyzes estrone sulfate (E1-S) and dehydroepiandrosterone sulfate (DHEA-S) to E1 and DHEA, respectively (**Figure 1**), as well as cholesterol sulfate and pregnenolone sulfate to their

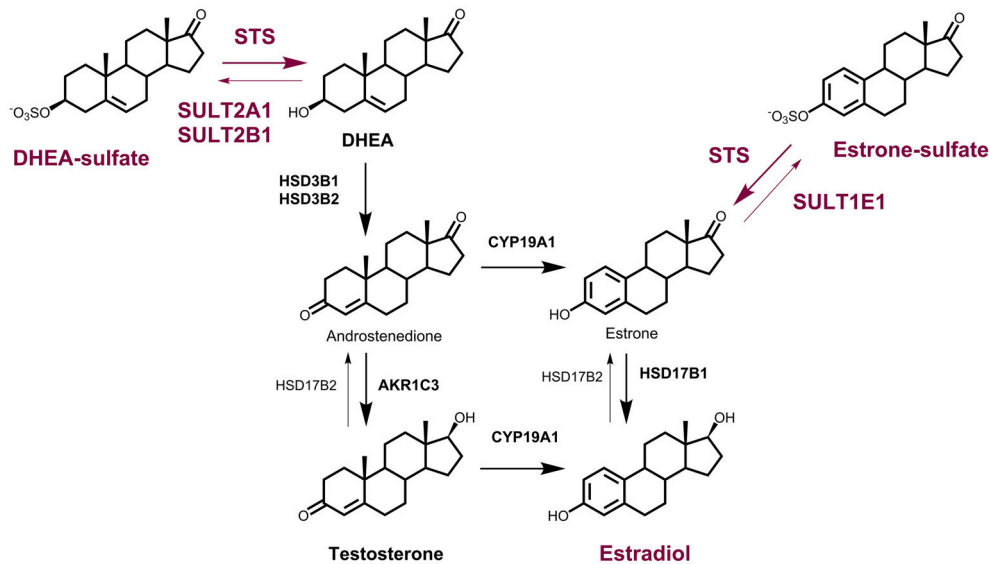


FIGURE 1 | The roles of the STS and SULT enzymes in local estrogen biosynthesis. Synthesis of E2 from DHEA-S by the action of steroid sulfatase (STS), 3β -hydroxysteroid dehydrogenase- Δ^4 -isomerase (HSD3B1, HSD3B2), aromatase (CYP19A1) and 17-ketosteroid reductase (HSD17B1) or aldo-keto reductase 1C3 (AKR1C3) and CYP19A1; and from E1-S by the action of STS and HSD17B1. Sulfotransferases 2A1 (SULT2A1) and SULT2B1 catalyze the conjugation of DHEA, and SULT1E1 catalyzes the conjugation of E1. Oxidation of E2 to E1 is catalyzed by HSD17B2.

corresponding unconjugated forms. The sulfatase protein family includes 17 different human sulfatases, where only STS act on steroid sulfates (Mueller et al., 2015).

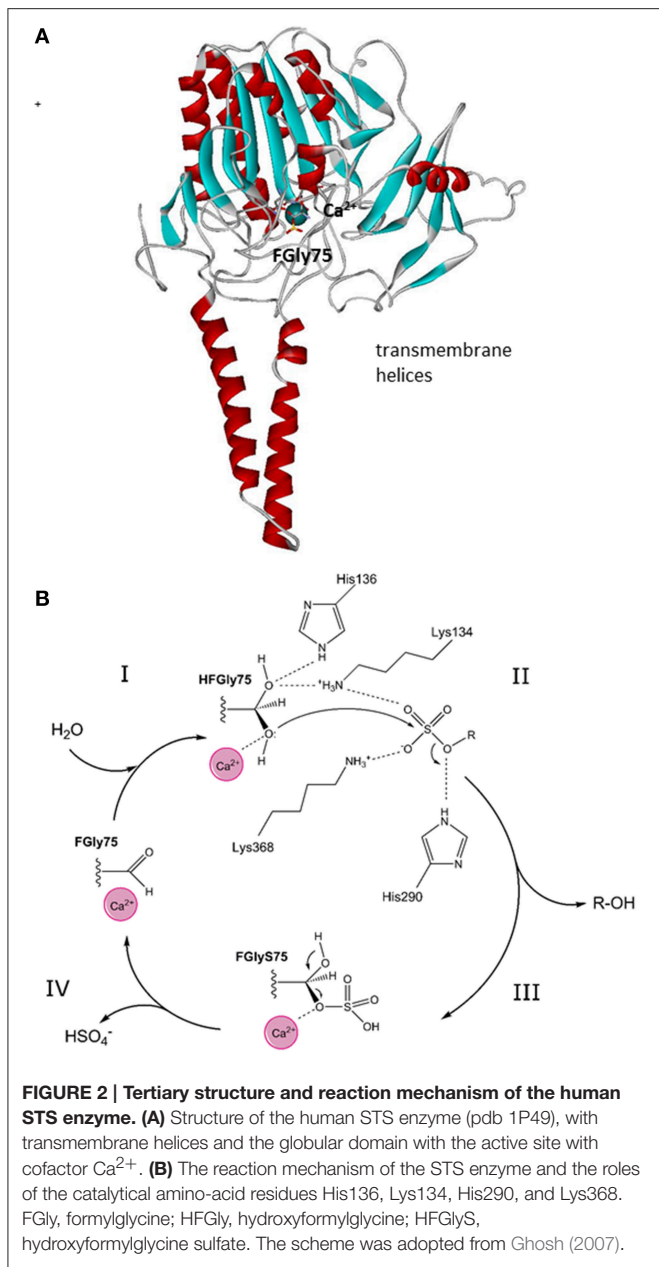
STS has been found in the membranes of the endoplasmic reticulum and was purified from human placenta (Hernandez-Guzman et al., 2001). It is a monomer with a molecular mass of 63 kDa, an N-terminal signal peptide of 21–23 amino acids, and four potential and two functional (i.e., Asn47, Asn259) glycosylation sites (Reed et al., 2005). Purified STS has been crystallized, and its structure has been defined at 2.6-Å resolution (pdb code 1P49; Hernandez-Guzman et al., 2001, 2003). The three-dimensional structure of STS shows a globular polar domain with the catalytic site, and the putative transmembrane domain that consists of two antiparallel hydrophobic alpha helices (Hernandez-Guzman et al., 2003) (Figure 2A). STS includes Ca^{2+} as a cofactor and 10 catalytically important amino acid residues: Arg35, Arg36, ARG78, Arg342, Lys134, Lys368, His136, His290, Gln343 and a formylglycine (FGly75). This posttranslational modification of Cys75 to FGly75 is mediated by the FGly-generating enzyme encoded by *sulfatase-modifying factor 1* (Preusser-Kunze et al., 2005).

STS catalyzes the hydrolysis of the sulfate moiety in a four-step mechanism. According to Ghosh (2007), these steps comprise: (1) activation of FGly75 by a water molecule; (2) nucleophilic attack of hydroxy-FGly on the sulfur atom of the substrate (i.e., E1-S, DHEA-S), which is facilitated by Ca^{2+} ; (3) release of the free hydroxy-product (i.e., E1, DHEA); and finally (4) release of HSO_4^- and regeneration of FGly (Figure 2B). As a sulfate moiety covalently linked to hydroxy-FGly has been observed in the crystal structure of STS, this suggests that the sulfated form of hydroxy-FGly is the resting state for human STS (Ghosh, 2007).

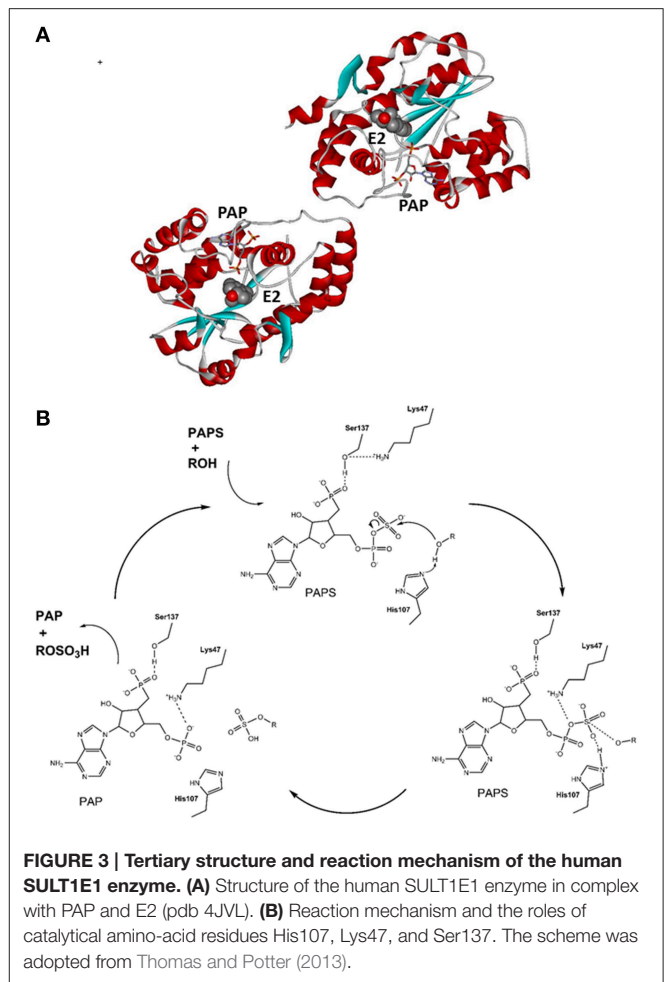
Kinetics characterization has revealed that purified STS can hydrolyze DHEA-S and E1-S with μM Km values (Hernandez-Guzman et al., 2001; Table 1).

The STS gene has been localized to the X chromosome (Xp22.31), and it spans 146 kb, includes 10 exons, and encodes a protein of 583 amino acids (Reed et al., 2005). Although eight tissue-specific STS transcripts have been identified (Nardi et al., 2009), only six are currently included in the gene database: isozyme S, and variants X1 to X5 (<http://www.ncbi.nlm.nih.gov/gene>). STS transcripts have 235 coding genetic variants (cSNPs) in the db SNP database (<http://www.ncbi.nlm.nih.gov/SNP>; September 2015), although only one of these cSNPs, Val307Ile, has a minor allele frequency (MAF) >0.01 (0.0172) (Table 2). SNPs have been reported in the promoter region and in introns and exons of the STS gene (Brookes et al., 2010; Matsumoto et al., 2010, 2013). Seven SNPs have been identified in the Japanese population, including one SNP in the 5'-untranslated region (155G>A), five in the 5'-flanking region, and one cSNP, Val476Met, with a frequency of 0.014 (Matsumoto et al., 2010). For three specific SNPs, functional analysis has revealed significantly decreased (155A) and increased (–2837A, –1588C) transcriptional activities in a reporter gene assay in MCF7 cells, but showed no effects at the protein and DHEAS STS activity levels for Val476Met variant (Matsumoto et al., 2013).

The loss of STS activity due to STS gene deletion or point mutations results in X-linked ichthyosis, a genetic skin disorder that affects 1 in 2000 to 1 in 6000 males and is characterized by typical scaling of the skin epidermis (Gelmetti and Ruggero, 2002). Interestingly, deletions and mutations have been identified mainly in the regions from 7 to 10 exon, which encodes the C-terminal substrate binding part (Gelmetti and Ruggero, 2002). This disease results from the inability to liberate cholesterol from



cholesterol sulfate, and it affects the incorporation of cholesterol sulfate in the stratum corneum. It is associated with epidermal hyperplasia and the formation of additional layers of corneocytes, which leads to unacceptable sloughing of the skin epidermis (Maltais and Poirier, 2011; Elias et al., 2014). Kent et al. reported that boys with this genetic disorder have a significantly increased risk of attention deficit hyperactivity disorder and autism (Kent et al., 2008). Interestingly, associations between this disorder and several SNPs within the *STS* gene were also reported (Brookes et al., 2010), where the SNP rs12861247 was significantly associated with lower *STS* expression. In contrast to these studies, Stergiakouli et al. did not confirm these associations, although they observed associations between the SNP rs17268988 and symptoms of inattention (Stergiakouli et al., 2011).



STS is ubiquitously expressed, with its highest protein levels in placenta, and lower levels in breast, skin, liver, lung, ovary, adrenal gland, endometrium, brain, and some other tissues. The tissue levels vary across physiological and pathophysiological conditions, but our current understanding of the regulation of *STS* expression is still very limited (Nardi et al., 2009). *STS* expression is under the control of estrogens in breast cancer (Zaichuk et al., 2007), and it is down-regulated by GnRH agonists (Maitoko and Sasaki, 2004) and danazol (Fechner et al., 2007) in endometriotic tissue. In endometrium, no significant differences in *STS* expression have been reported at the mRNA level between the proliferative and secretory phases (Colette et al., 2013), while at the protein level, significant down-regulation was seen in the late secretory phase, compared to the menstrual phase (Dassen et al., 2007). *STS* expression can also be affected by the inflammatory cytokines: interleukin (IL)1 α enhanced *STS* expression and mRNA levels in the SKOV3 epithelial ovarian cancer cell line, but not in the OSE normal ovarian surface epithelium cell line (Ren et al., 2015), and IL1 β suppressed *STS* expression in endometrial stromal cells (Matsuoka et al., 2002). On the other hand, IL6 and tumor necrosis factor (TNF) α increased *STS* activity in a breast cancer cell line MCF7 not changing the mRNA levels, which suggested posttranslational

TABLE 1 | Kinetics characteristics of the STS and SULT enzymes.

| Enzyme | Substrate | K _m | V _{max} | V _{max} /K _m | K _i | References |
|-----------------------|-----------|----------------|----------------------|----------------------------------|----------------|--|
| STS | DHEA-S | 9.6 μM | 113.4 μmol/h/mg | 11.9 | | Hernandez-Guzman et al., 2001 ^a |
| | E1-S | 72.8 μM | 573 μmol/h/mg | 7.9 | | Hernandez-Guzman et al., 2001 ^a |
| SULT1E1 | E1 | 110 ± 100 nM | 4.1 ± 0.1 nmol/h/mg | 0.04 | | Adjei et al., 2003 ^b |
| | E2 | 29 ± 10 nM | 6.9 ± 0.1 nmol/h/mg | 0.24 | | Adjei et al., 2003 ^b |
| SULT2A1 | DHEA | 2.5 ± 0.7 μM | 13.6 ± 2.5 μmol/h/mg | 5.4 | 6.1 μM | Lu et al., 2008 ^b |
| SULT2B1a [*] | DHEA | 2.3 ± 0.2 μM | 0.3 ± 0.01 μmol/h/mg | 0.13 | 48 μM | Geese and Raftogianis, 2001 ^b |
| SULT2B1b [*] | DHEA | 4.4 ± 0.6 μM | 0.1 ± 0.01 μmol/h/mg | 0.02 | 22 μM | Geese and Raftogianis, 2001 ^b |

^aPurified STS from human placenta.

^bPurified recombinant human enzymes, mean ± SEM values are shown; ^{*}SULT2B1a and SULT2B1b are two isoforms.

TABLE 2 | Different transcripts and genetic variants of the STS and SULT genes.

| Gene | Gene | Transcript | Size | Protein | gSNP | cSNP | | |
|---------|------|------------------------|------|---------|------|-------|-----|---------------------------------------|
| | ID | information | (bp) | (aa) | | Total | SYN | MAF >0.01 |
| STS | 412 | Isozyme SNM_000351.4 | 6377 | 583 | 4838 | 231 | 93 | Val307Ile, 0.0172 |
| | | Variant X5XM_011545518 | 6340 | 578 | 3772 | 231 | 93 | Val307Ile, 0.0172 |
| | | Variant X4XM_011545517 | 6215 | 578 | 3782 | 231 | 93 | Val307Ile, 0.0172 |
| | | Variant X3XM_011545516 | 6662 | 590 | 7324 | 232 | 93 | Val307Ile, 0.0172 |
| | | Variant X2XM_011545515 | 7336 | 590 | 7365 | 235 | 93 | Val307Ile, 0.0172 |
| | | Variant X1XM_005274511 | 6441 | 723 | 7318 | 232 | 93 | Val307Ile, 0.0172 |
| SULT1E1 | 6783 | Variant X2XM_011532210 | 723 | 181 | 911 | 88 | 23 | – |
| | | Variant X1XM_011532209 | 1697 | 294 | 1337 | 156 | 42 | – |
| | | NM_005420 | 1805 | 294 | 1300 | 156 | 42 | – |
| SULT2A1 | 6822 | NM_003167 | 1987 | 285 | 1207 | 163 | 48 | Ala63Pro, 0.0240 Ala261Thr, 0.0407 |
| SULT2B1 | 6820 | Variant 2NM_177973 | 1228 | 365 | 3190 | 231 | 88 | Arg33Gln, 0.0178 |
| | | Variant X1XM_005259182 | 802 | 221 | 935 | 153 | 57 | – |
| | | Variant 1NM_004605 | 1281 | 350 | 1707 | 220 | 82 | Arg18Gln, 0.0178 |

gSNP, SNP in gene region; cSNP, SNP within coding region; SYN, synonymous; MAF, minor allele frequency; data from Gene and SNP databases (<http://www.ncbi.nlm.nih.gov/gene>, <http://www.ncbi.nlm.nih.gov/SNP>); as of September 2015.

modifications *via* STS glycosylation (Newman et al., 2000). In contrast, Sung et al. recently reported that in prostate cancer cell line PC-3 both, TNF α and insulin growth factor II regulate STS expression at the transcriptional level (Sung et al., 2013). STS expression is also regulated by micro (mi)RNA, as the overexpression of miR-142-3p significantly reduced STS mRNA levels in the St-T1b human endometrial stromal cell line (Kästingschäfer et al., 2015).

STEROID SULFOTRANSFERASES

The SULTs catalyze the transfer of a sulfuryl group from 3'-phosphoadenosine-5'-phosphosulfate (PAPS) to the target molecule. This conjugation is typically involved

in inactivation/detoxification reactions for a variety of substrates, such as xenobiotics, therapeutic drugs, toxic compounds, chemical carcinogens, bile acids, hormones and neurotransmitters, and it is also an important pathway for hormonal regulation (Geese and Raftogianis, 2001). The superfamily of cytosolic human SULTs comprises 13 *SULT* genes and spans four families: SULT1 includes three phenol SULT subfamilies (SULT1A, SULT1B, SULT1C) and an estrogen SULT (SULT1E1); SULT2s catalyze sulfonation of the hydroxyl groups of steroids (SULT2A1, SULT2B1); and there are two orphan SULT families, SULT4 and SULT6 (SULT4A1, SULT6B1) (reviewed in Geese and Raftogianis, 2001; Lindsay et al., 2008). SULT2A1 catalyzes the sulfonation of DHEA, androgens and estrogens, while SULT2B1 catalyzes sulfonation of only DHEA (Lindsay et al., 2008). Although SULTs in general have broad

substrate specificity, *SULT1E1* (E.C. 2.8.2.4.) has significantly greater affinity for the estrogens than other *SULTs*, and it inactivates E1 and estradiol (E2) with nM K_m values (Falany et al., 1995; **Table 1**). *SULT2A1* (E.C. 2.8.2.14) and *SULT2B1* (E.C. 2.8.2.2) both catalyze sulfation of DHEA, although *SULT2A1* shows much higher catalytic efficiency (Lu et al., 2008). The *SULTs* need PAPS as a coenzyme, and thus *SULT* expression has to be accompanied by expression of at least one of the two PAPS synthase genes (Mueller et al., 2015).

The *SULT1E1* gene has been localized to chromosome 4 (4q13.2), it has eight exons and a length of 20 kb, and it encodes a protein of 294 amino acids with a molecular mass of 35 kDa (Falany et al., 1995). Recombinant *SULT1E1* has been crystallized, and the structure of the binary complex with PAPS (pdb code 1HY3; Pedersen et al., 2002) and several ternary complexes, including a complex with PAP and E2 (pdb code 4JVL; Gosavi et al., 2013), have been resolved. *SULT1E1* is a dimer with an α/β motif that consists of five parallel β -strands surrounded by α -helices and a conserved α -helix across this structure (Pedersen et al., 2002) (**Figure 3A**). The structure of the *SULT1E1*-PAP-E2 complex has revealed that E2 binds to a mostly buried hydrophobic pocket with the sulfuryl acceptor 3' hydroxyl within H-bonding distance of the proposed catalytic His107, and Lys10. The Phe80 and Phe141 are involved in the positioning of the steroidal substrate and have been suggested to function as a steric gate, thus defining substrate specificity (Gosavi et al., 2013). *SULT1E1* has three catalytic amino-acid residues: Lys47, His107, and Ser137 (Negishi et al., 2001). The proposed reaction mechanism is as follows: upon binding of PAPS, Ser137 forms an H-bond with Lys47, thus prevents its interaction with the bridging oxygen in PAPS and its further hydrolysis; His107 attracts a proton from the substrate hydroxyl (i.e., of E2, DHEA), and enables nucleophilic attack at the sulfur atom in PAPS. In the next step, Lys47 interacts with the 5' phosphate of PAPS, which help in dissociation of the sulfuryl group and in its transfer to the substrate. Finally, the reaction products, PAP and E1-S are released, which completes the catalytic cycle (Gamage et al., 2006; Tibbs et al., 2015) (**Figure 3B**). The crystallization and kinetics data have further suggested that the substrate inhibition that has been observed at high concentrations is a dead-end complex where both PAP and E2 are bound (Gosavi et al., 2013).

For the *SULT1E1* gene, in addition to the primary transcript, there are two variant transcripts (i.e., variants X1, X2) that encode proteins of 294 amino acids and 181 amino acids. Currently more than 150 cSNPs are included in the SNP database for *SULT1E1*, but none show $MAF > 0.01$ (**Table 2**). Functional analysis has revealed decreased *SULT1E1* activities for two nonsynonymous coding SNPs: Asp22Tyr and Ala32Val (Adjei et al., 2003). These cSNPs were found in African-American (Asp22Tyr) and Caucasian (Ala32Val) populations (Adjei et al., 2003). Additionally, the SNP rs6259 in the promoter region of *SULT1E1* has been associated with increased risk of endometrial cancer (Rebbeck et al., 2006; Hirata et al., 2008), and SNPs *959 G>A and IVS4-1653 T>C with increased recurrence of endometrial cancer (Choi et al., 2005).

SULT1E1 is expressed in liver, secretory endometrium, fetal liver, lung, and kidney (Coughtrie, 2002). Expression of *SULT1E1*

is regulated by steroid hormones. In the normal endometrium, the highest expression of *SULT1E1* was found for the secretory phase, which is consistent with regulation by progesterone (Falany and Falany, 1996; Rubin et al., 1999; Dassen et al., 2007), although Colette et al. recently reported that *SULT1E1* expression is unchanged in the proliferative and secretory phases (Colette et al., 2013). In endometrial cancer cell line Ishikawa *SULT1E1* is induced by steroid drug tibolone via progesterone receptor (Falany and Falany, 2006), while in liver it is repressed by xenobiotic activators of the pregnane X receptor and aryl hydrocarbon receptor peroxisome proliferator, and activated via peroxisome proliferator activated receptor α and the liver X receptor (Duanmu et al., 2007). Furthermore, studies have implied that *SULT1E1* is also epigenetically regulated, as its expression is induced by the histone deacetylase inhibitor trichostatin A in MCF10A cells (Fu et al., 2010). *SULT1E1* activity is also affected by ubiquitous pollutants, such as the polychlorinated biphenyls, which act as potent inhibitors with K_i values in the pM range, and thus they can exert their endocrine disrupting effects without binding to steroid hormone receptors (Kester et al., 2000).

The *SULT2A1* gene has been localized to chromosome 19 (19q13.3). It has six exons and a total length of 16 kb (Freimuth et al., 2004), with only one transcript known, which encodes a protein with 285 amino acids and a molecular mass of 34 kDa (**Table 2**). Several crystal structures of *SULT2A1* binary complexes have been resolved (Tibbs et al., 2015), including complexes with DHEA (pdb code 1J99; Rehse et al., 2002) and PAPS (pdb code 4IFB). The complete kinetic mechanism of *SULT2A1* has been defined, which revealed that the binding of DHEA and PAPS is random, while the rate-limiting step is nucleotide release. Here, the potent substrate inhibition with a K_i of 6.1 μ M for DHEA can be explained by trapping PAP in a dead-end complex, which impedes the release of the nucleotide coenzyme (Wang et al., 2014).

SULT2A1 is expressed in liver, adrenal gland, fetal adrenal, and fetal liver (Luu-The et al., 1995; Coughtrie, 2002). *SULT2A1* has broad substrate specificity, as it can catalyze sulfonation of many hydroxysteroids, including DHEA, epiandrosterone, androsterone, testosterone, E2, cholesterol, various bile acids, pregnenolone, 17-ethinyl-E2 and cortisol (Lindsay et al., 2008). More than 160 cSNPs have been reported for *SULT2A1* (**Table 2**). Functional analysis has revealed that the nonsynonymous SNPs Met57Thr, Glu186Val, Ala63Pro, and Lys227Glu result in decreased *SULT2A1* activity when expressed in COS-1 cells (Nagata and Yamazoe, 2000). Interestingly, the *SULT2A1* SNPs Ala63Pro, Lys227Glu and Ala261Thr have only been found in African-American populations, and these might explain the reported interethnic differences in *SULT2A1* activity (Thomae et al., 2002; Hildebrandt et al., 2007). The *SULT2A1* SNP Ala261Thr has an allele frequency of 13% in African-American populations (reported MAF , 0.0407) and is located within the dimerization motif, where it prevents formation of *SULT2A1* dimers. Surprisingly Ala261Thr still has 93% of the wild-type enzyme activity. Also Ala63Pro is quite common, with an allele frequency of 5% in African-American populations, and a reported MAF of 0.024 (**Table 2**).

The expression of *SULT2A1* is regulated at the transcriptional level by the constitutive androstane receptor and pregnane X receptor (Echchgadda et al., 2007). As recently shown in human hepatocytes and the HepG2 cell line, the *SULT2A1* gene is induced by E2 activation of estrogen receptor (ER) α via classical, direct binding to the estrogen response element, and via nonclassical, AP-1-mediated mechanisms (Li et al., 2014). *SULT2A1* appears to be regulated also at the epigenetic level, as shown by induction of *SULT2A1* expression after treatment of MCF7 cells with a histone deacetylase inhibitor (Fu et al., 2010). In the adrenal gland, the expression of *SULT2A1* depends on two transcription factors: steroidogenic factor 1 and GATA-6 (Saner et al., 2005).

The SULT2B1 isoforms SULT2B1a and SULT2B1b are products of alternative transcriptional initiation and mRNA splicing of the same gene, and are expressed in different tissues. SULT1B1a is expressed in colon, ovary, and fetal brain, and SULT2B1b in liver, colon, small intestine, placenta, ovary, uterus, and prostate (Geese and Raftogianis, 2001). SULT1B1a and SULT1B1b, which has an additional 23 N-terminal amino-acid residues, have been cloned and expressed in prokaryotic and eukaryotic systems, and purified and characterized (Geese and Raftogianis, 2001; Meloche and Falany, 2001). These enzymes catalyze sulfonation of 3 β -hydroxysteroids, pregnenolone, 17 α -hydroxypregnenolone and DHEA (Geese and Raftogianis, 2001). The structures of both SULT2B1a and SULT2B1b in binary complexes with PAP (pdb codes 1Q1Q, 1Q1Z, respectively Lee et al., 2003) have been resolved, as have two ternary complexes of SULT1Bb with PAP and pregnenolone (pdb code 1Q2O; Lee et al., 2003), and with PAP and DHEA (pdb code 1Q22, Lee et al., 2003; Tibbs et al., 2015).

The *SULT2B1* gene has been localized to chromosome 19 (19q13.3), and it comprises six exons with a total length of 48 kb (Geese and Raftogianis, 2001; Meloche and Falany, 2001; Freimuth et al., 2004). Three transcripts have been identified (variants 1, 2, X1) that encode proteins of 350, 365, and 221 amino acids (Table 2). Although more than 200 coding SNPs for *SULT2B1* are currently included in the SNP database, there is only one nonsynonymous SNP: Arg33Gln, with MAF >0.01 (Table 2). So far, only a few of these SNPs have been studied in more detail. Recently, Lévesque et al. (2014) reported that *SULT2B1* SNPs rs12460535, rs2665582, and rs10426628 are significantly associated with prostate cancer progression and hormone levels.

The SULT enzymes are known to show profound substrate inhibition, and SULT2B1 is not an exception. DHEA inhibits SULT2B1a and SULT2B1b with K_i values of 48 μ M and 22 μ M, respectively (Geese and Raftogianis, 2001). Not much is known about the regulation of *SULT2B1*. In normal endometrium, higher SULT2B1b mRNA levels have been seen in the mid-luteal phase, in agreement with progesterone regulation (Koizumi et al., 2010). In human endometrial stromal cells, the levels of SULT2B1b transcript were increased by cAMP or progesterone, while they were increased by cAMP or relaxin in endometrial epithelial cells, stimulating protein kinase A pathway (Koizumi et al., 2010). In prostate cancer cells, expression of SULT1B1b was shown to be regulated by vitamin D via heterodimer of vitamin D receptor and retinoid X receptor α (Seo et al., 2013).

LOCAL PRODUCTION OF ESTROGENS FROM DHEA-S AND E1-S

STS and SULTs have pivotal roles in estrogen synthesis in peripheral tissues, and thus also in pre-receptor regulation of steroid hormone action. In premenopausal women, estrogens can be synthesized in the ovaries and in peripheral tissues (Labrie, 1991; Simpson, 2003). After menopause, when the ovaries cease to act, estrogens are formed only in the peripheral sites, which mainly include adipose tissue, but also bone, vascular endothelium, aortic smooth muscle cells, and brain (Simpson, 2003). Locally, estrogens can be formed from the inactive precursors of adrenal origin, DHEA-S, DHEA, and androstenedione, and of ovarian origin, DHEA and androstenedione, or from circulating E1-S (Figure 1). These steroid precursors are at relatively high concentrations in the blood of premenopausal and postmenopausal women, with DHEA-S at $3.4 \pm 1.7 \mu$ M and $1.6 \pm 1.0 \mu$ M, respectively (Labrie et al., 2006). DHEA and androstenedione are at 15.5 ± 7.6 nM and 3.4 ± 1.2 nM respectively, in premenopausal women, and 6.8 ± 4.1 nM and 1.4 ± 0.6 nM, respectively, in postmenopausal women (Labrie et al., 2006). Estrogens can thus be produced via the so-called aromatase pathway, from androstenedione and testosterone, by the actions of aromatase and 17-ketosteroid reductases (i.e., 17 β -hydroxysteroid dehydrogenases; HSD17B), mainly HSD17B1. Estrogens can also be formed from DHEA-S by the actions of STS, 3 β -hydroxysteroid dehydrogenases- Δ^4 -isomerase (HSD3B1, HSD3B2), aromatase (CYP19A1) and HSD17B or aldo-keto reductase 1C3 (AKR1C3) and CYP19A1, and from E1-S by the actions of STS and HSD17B (Rižner, 2013; Figure 1). The formation of E2 from E1-S is known as the STS pathway. E1-S is the most important estrogen in the peripheral blood, at 1.8 ± 1.1 nM and 0.6 ± 0.03 nM in premenopausal and postmenopausal women, respectively (Caron et al., 2009; Labrie et al., 2009). Studies in breast and endometrial cancers have shown that the STS pathway prevails over the aromatase pathway (Pasqualini et al., 1996; Chetrite et al., 2000; Purohit et al., 2011; Rižner, 2013). Higher E1-S, E1, and E2 plasma concentrations were observed for patients with breast cancer and endometrial cancer, compared to control women (Lépine et al., 2010; Tworoger et al., 2014) and high E1-S and E2 have been measured in breast cancer tissue (Chetrite et al., 2000), with high E2 and a high E2 to E1-S ratio reported in endometrial cancer tissue (Naitoh et al., 1989; Berstein et al., 2003). Most importantly, the levels of estrogens in breast and endometrial cancer tissue are 2- to 40-fold higher compared to plasma concentrations (Pasqualini et al., 1996; Berstein et al., 2003), further supporting intracrine formation and actions of estrogens.

DHEA-S and E1-S can thus serve as precursors for E2 formation after their translocation into cells via the transporter proteins of the organic anion-transporting polypeptide and organic anion-transporter families (Mueller et al., 2015). STS can then hydrolyze DHEA-S and E1-S to DHEA and E1, respectively, while the SULTs can catalyze the reverse reactions. SULT1E1 inactivates E1 and E2 to form the corresponding sulfates, and SULT2A1 and SULT2B1 conjugate DHEA (Raftogianis et al., 2000; Meloche and Falany, 2001; Gamage et al., 2006; Pasqualini,

2009). The sulfated steroids can then be excreted from the cells via the ABC transporters (Mueller et al., 2015). The resulting increased uptake together with the decreased excretion of DHEA-S and E1-S, and the disturbed delicate balance between the STS and SULT enzymes, might thus lead to increased levels of estrogens, which are associated with hormone-dependent diseases, including several gynecological diseases.

SULFATASE AND SULFOTRANSFERASES IN GYNECOLOGICAL DISEASES

Benign gynecological diseases such as endometriosis, adenomyosis, and uterine fibroids, and gynecological cancers such as endometrial cancer and ovarian cancer, affect a large proportion of women. The benign diseases are associated with infertility, and they can significantly decrease quality of life, while gynecological cancers comprise more than 10% of cancer-related deaths in women worldwide (Ferlay et al., 2013). These diseases are mainly hormone-dependent and thus rely on the local formation of active steroid hormones.

Sulfatase and Sulfotransferase in Endometriosis

Endometriosis is a frequent benign gynecological disease that is characterized by the presence of endometrial tissue outside the uterine cavity. In the general population of women of reproductive age, the predicted prevalence of endometriosis is 6–10%, but the frequency increases to 30–50% in women with pain, infertility, or both (Guo and Wang, 2006; Rogers et al., 2013). Ectopic endometrial tissue can be found in different

parts of the peritoneal cavity, where these locations define three different entities with different etiologies and pathogenesis: ovarian, peritoneal, and deep infiltrating endometriosis (Brosens and Benagiano, 2011). Endometriosis is an estrogen-dependent disease where endometriotic tissue proliferates in response to systemic estrogens and estrogens formed locally through the aromatase and the sulphatase pathways (Huhtinen et al., 2009; Rižner, 2009). However, the STS pathway appears to outperform the aromatase pathway, as the aromatase activity in endometriotic tissue is negligible when compared to STS activity (Purohit et al., 2008; Delvoux et al., 2009).

Data on expression of STS in endometriosis have remained relatively contradictory (Table 3). Although metabolism studies have revealed significantly lower STS activity in ectopic than eutopic endometrium of patients with ovarian endometriosis (Carlström et al., 1988), significantly higher levels of STS mRNA were seen for samples of ovarian endometriosis compared to eutopic endometrium from control patients (Smuc et al., 2007, 2009). Also, in peritoneal endometriosis, STS activity was lower in ectopic than matched eutopic endometrium, but it still correlated with severity of disease and was higher in moderate/severe disease vs. minimal/mild disease (Purohit et al., 2008). At the mRNA level, Collette et al. observed no significant differences between peritoneal endometriosis (ectopic) and control (eutopic) endometrial tissue but found higher levels in deep infiltrating endometriosis compared to ovarian endometriosis (Colette et al., 2013). Deep infiltrating endometriosis, Dassen et al. found no differences in STS expression between ectopic and eutopic endometrium of patients and the normal endometrium of the control group, while they found significantly lower protein levels of STS in epithelial cells

TABLE 3 | Expression of STS and SULTs in endometriosis.

| Gene | Level | Regulation | References |
|---------|-----------------|--|---|
| STS | mRNA | ↑ OE/control endometrium ≈ DIE/eutopic/normal endometrium ↑ DIE/OE; ≈ PE/OE/eutopic endometrium | Smuc et al., 2007, 2009 Dassen et al., 2007 Colette et al., 2013 |
| | Protein | ↓ eutopic/normal endometrium ≈ ectopic/eutopic endometrium | Dassen et al., 2007 Colette et al., 2013 |
| | Activity (E1-S) | ↓ ectopic/eutopic ↓ PE/eutopic endometrium ↑ moderate/severe/minimal/mild ≈ ectopic/eutopic/control endometrium | Carlström et al., 1988 Purohit et al., 2008 Purohit et al., 2008 Delvoux et al., 2009 |
| SULT1E1 | mRNA | ≈ OE/control endometrium ↑ DIE/normal endometrium ≈ DIE, OE, PE/eutopic endometrium ↓ OE/normal endometrium ↓ OE/eutopic endometrium | Smuc et al., 2007, 2009 Dassen et al., 2007 Colette et al., 2013 Hevir et al., 2013 Borghese et al., 2008 |
| | Protein | ≈ OE, PE/eutopic/control endometrium | Hudelist et al., 2007 |
| SULT2B1 | mRNA | ↓ OE/normal endometrium | Hevir et al., 2013 |

OE, ovarian endometriosis; PE, peritoneal endometriosis; DIE, deep infiltrating endometriosis.

of eutopic endometrium compared to normal endometrium (Dassen et al., 2007). Delvoux et al. reported unchanged STS activity in samples from all three types of endometriosis (Delvoux et al., 2009). However, Purohit et al. reported that STS activity in peritoneal ectopic implants and matched eutopic endometrium was higher than aromatase activity, which thus suggested that the STS pathway is important in estrogen formation and that STS inhibitors might be useful for treatment of endometriosis (Purohit et al., 2008; Delvoux et al., 2009).

In addition to STS, SULTs should also be taken into account when evaluating the importance of the STS pathway, as both of these enzymes affect the subtle balance between estrogen activation (E1-S hydrolysis) and estrogen inactivation (E1, E2 sulfation). Expression of *SULTs* has been investigated in several studies (Table 3). In ectopic tissue of patients with ovarian, peritoneal, and deep infiltrating endometriosis, no significant differences in the expression of *SULT1E1* was seen at the mRNA level (Smuc et al., 2007, 2009; Colette et al., 2013), while there were significantly higher mRNA levels in ectopic endometrium of deep infiltrating endometriosis, when compared to the normal endometrium (Dassen et al., 2007). On the other hand, Borghese et al. and Hevir et al. found decreased mRNA levels in ovarian endometriosis vs. control eutopic endometrium from patients (Borghese et al., 2008) and control normal endometrium (Hevir et al., 2013), respectively. At the protein level, Hudelist et al. saw no differences between ovarian and peritoneal endometriotic lesions and eutopic endometrium (Hudelist et al., 2007). The expression of *SULT2A1* has not been studied in this context, but the expression of *SULT2B1* at the mRNA level was decreased in ovarian endometriosis compared to normal endometrium (Hevir et al., 2013); which implies that DHEA-S may serve as a precursor steroid in this ectopic tissue.

Data on the expression of the *STS* and *SULT* genes at the mRNA, protein and enzymatic activity levels in endometriosis tissue vs. control tissue are contradictory and do not fully support the importance of the sulfatase pathway. As different types of endometriosis show variations in the expression of these genes, it seems that the sulfatase may have roles primarily in ovarian endometriosis. Furthermore, the majority of studies have compared endometriotic tissue with eutopic endometrium of the same patient, which might not be the optimal study design. Nowadays, it is generally accepted that eutopic endometrium of endometriosis patients has already undergone pathological transformations, and that the gene expression profile in this tissue can be used as a biomarker of endometriosis (Burney et al., 2007).

Sulfatase and Sulfotransferase in Adenomyosis

Adenomyosis is a benign gynecological disease that is defined as the presence of endometrial glands and stroma within the muscular layer of the uterus (i.e., myometrial tissue) (Kitawaki, 2006; Graziano et al., 2015). The symptoms that appear in two-thirds of patients with adenomyosis are dysmenorrhea, metrorrhagia, chronic pelvic pain, dyspareunia, and infertility. The prevalence of adenomyosis varies among studies, with 5–70% reported (Graziano et al., 2015). Adenomyosis mainly affects

TABLE 4 | Expression of STS in adenomyosis.

| Gene | Level | Regulation | References |
|------|-----------------|---|-----------------------|
| STS | Protein | ↑ adenomyotic tissue/basilar layer of endometrium | Ezaki et al., 2001 |
| | Activity (E1-S) | ↑ STS ↓ danazol treatment | Yamamoto et al., 1993 |

women in late reproductive age and regresses after menopause (Kitawaki, 2006). It is thus considered an estrogen-dependent disease, and is often associated with other estrogen-dependent pathologies, such as endometriosis, leiomyoma, and hyperplasia, and also with endometrial cancer (Kitawaki, 2006). Furthermore, expression of aromatase in adenomyotic tissue is also implicative of estrogen dependency (Kitawaki et al., 1997). However, the STS pathway for the local formation of estrogens has been studied by only two groups (Table 4). Ezaki et al. observed increased STS protein levels in adenomyotic tissue vs. the basilar layer of normal endometrium (Ezaki et al., 2001), and Yamamoto et al. reported increased E1-S STS activity in adenomyosis, which was reduced by danazol treatment (Yamamoto et al., 1993). Although the involvement of estrogens in the pathophysiology of adenomyosis has not been sufficiently studied, and thus further investigations into estrogen biosynthesis and actions in this gynecological disease are warranted, the published data indicates importance of the sulfatase pathway.

Sulfatase and Sulfotransferase in Uterine Fibroids

Uterine fibroids (leiomyomas; *myoma uteri* or *uterus myomatosus*) are benign tumors of the myometrium that occur in up to 70% of women of reproductive age (Bulun, 2013). However, the clinically significant symptoms that include heavy menstrual bleeding, anemia, difficulties with conceiving, and increased risk of miscarriage, are seen in one-third of the affected population (Bulun, 2013). Uterine fibroids appear after menarche and decline after menopause, which implicates the estrogens as the primary factor that drives their growth. Additionally, studies showed that estrogens are necessary, but not sufficient for proliferation and progesterone also has an important role in growth of leiomyomas. Estrogens act via estrogen receptor α and thus stimulate expression of progesterone receptors and further pro-proliferative action of progesterone (Moravek et al., 2015).

Based on PubMed searches, there has been only one report on the STS pathway in myoma tissue (Table 5). The Okada group examined E1-S hydrolysis and E1 sulfation in myoma tissue vs. myometrium, and they showed decreased STS and increased SULT activities (Yamamoto et al., 1990, 1993), thus suggesting that more estrogens can be formed in the surrounding myometrium than in the myoma tissue. In this way, estrogens might still act in a paracrine manner to provide myoma tissue with the mitogenic E2. As other studies showed that aromatase is upregulated, the local estrogen formation via the aromatase pathway probably has more important role. Furthermore, the effects of gonadotropin-releasing hormone analogs on the levels of estrogens and STS activity have also been examined in myoma

TABLE 5 | Expression of STS and SULT in myoma uteri.

| Gene | Level | Regulation | References |
|----------------|-----------------|------------------------|-----------------------|
| STS | Activity (E1-S) | ↓ myoma vs. myometrium | Yamamoto et al., 1990 |
| <i>SULT1E1</i> | Activity (E1) | ↑ myoma vs. myometrium | Yamamoto et al., 1990 |

where lower levels of estrogens (Pasqualini et al., 1990; van de Ven et al., 2002) and no significant effects on STS activity (van de Ven et al., 2002) were seen. So far the roles of the sulfatase pathway in uterine fibroids have not been thoroughly examined, which calls for further studies.

Sulfatase and Sulfotransferase in Endometrial Cancer

Endometrial cancer is the most common gynecological malignancy in the developed world. Worldwide, 319,605 new cases of endometrial cancer and 76,160 deaths were estimated for 2012 (Ferlay et al., 2013). Based on histopathology, the majority of endometrial cancers can be divided into two groups: type 1 with an endometrioid histology, which comprises 70–80% of all cases (Yeramian et al., 2013); and type 2 with serous papillary or clear-cell histology, which comprise 20% of all cases. Type 1 endometrial cancer is considered to be estrogen dependent, and type 2 not to be associated with hyper-estrogenic factors (Amant et al., 2005; Ryan et al., 2005). Development of type 1 endometrial cancer is usually explained by the unopposed estrogen hypothesis, which proposes that exposure to estrogens (of either endogenous or exogenous origins) that is not opposed by progesterone or synthetic progestins increases the mitotic activity of endometrial cells and the number of DNA replication errors. This can lead to somatic mutations that can result in malignant phenotypes (Henderson and Feigelson, 2000; Akhmedkhanov et al., 2001; Inoue, 2001; Sonoda and Barakat, 2006). In line with intracrine estrogen action the formation of estrogens has been detected in proliferative and secretory endometrium and in endometrial cancer tissues (Tseng et al., 1982). Additionally, increased E2 concentrations have been reported in cancerous endometrium of premenopausal and postmenopausal women with type 1 and type 2 endometrial cancer (Bonney et al., 1986; Berstein et al., 2003), and higher E1-S plasma concentrations were observed for endometrial cancer patients, compared to control healthy postmenopausal women (Jasonni et al., 1984).

Expression of STS and its activity in endometrial cancer have been evaluated in nine studies (Table 6). No significant differences in STS expression (Smuc and Rizner, 2009) and increased mRNA levels of STS (Lépine et al., 2010) have been reported in endometrial cancer vs. adjacent control tissue. At the cellular level, STS immunoreactivity in endometrial cancer tissue was higher compared to normal endometrium (Utsunomiya et al., 2004), which suggests increased availability of the biologically active estrogens. In line with this, immunohistochemical data and early metabolism studies have shown significantly higher E1-S STS activity in endometrial cancer tissue, compared to control endometrium

(Adessi et al., 1984; Prost et al., 1984; Naitoh et al., 1989; Urabe et al., 1989). However, more recently, Tanaka et al. reported lower E1-S STS activity in cancerous tissue, compared to normal endometrium (Tanaka et al., 2003). This discordance might be explained by the different control groups or menopausal stages of the cases and controls. Increased DHEA-S STS activity has also been observed in endometrial cancer, compared to normal endometrium (Abulafia et al., 2009).

In cancerous and adjacent control endometrium, *SULT1E1* mRNA levels were reported to be unchanged or borderline significantly up-regulated (Lépine et al., 2010; Hevir et al., 2011; Table 6). The study by Lépine et al. (2010) included 26% type 2 endometrial cancer patients, which might explain these differences observed. At the cellular level, *SULT1E1* immunoreactivity was diminished (Utsunomiya et al., 2004) or was not detected (www.proteinatlas.org; Uhlén et al., 2015) in endometrial cancer, compared to normal endometrium, while in other studies, increased *SULT1E1* staining has been observed in cancerous endometrium, compared to adjacent control endometrium (Xu et al., 2012). These differences can be explained by different antibodies used. As *SULT2A1* is not expressed in either endometrial cancer or adjacent control endometrium (Rubin et al., 1999), *SULT2B1* is the major DHEA-specific SULT enzyme in endometrial cancer, and increased *SULT2B1* expression has recently been reported in endometrial cancer, compared to adjacent control endometrium (Hevir et al., 2011). Also Human Protein Atlas data show medium to high staining of cancerous endometrium with two different anti-*SULT2B1* antibodies (Uhlén et al., 2015), which further supports the conclusion that despite of increased DHEA-S STS activity, DHEA-S may not represent the steroid precursor for E2 formation in cancerous endometrium.

Although the expression of the STS and *SULT1E1* genes in diseased vs. control endometrium has differed between studies (Table 6), all of the published data show higher mRNA and protein levels for STS than *SULT1E1* in endometrial cancer tissue vs. control endometrium. The majority of the published data also shows increased E1-S STS activity in endometrial cancer, and thus supports E2 formation via the STS pathway.

Sulfatase and Sulfotransferase in Ovarian Cancer

Ovarian cancer is the sixth leading cause of cancer-related death in the developed world. Worldwide, there were 238,719 new cases and 151,905 deaths estimated for 2012 (Ferlay et al., 2013). Most patients are diagnosed when they show advanced stage disease with poor prognosis. Ovarian cancer is a heterogeneous disease that encompasses several types of tumors, with large differences in histopathological features and clinical behaviors. Epithelial ovarian cancers are the most frequent tumors, which account for around 98% of all cases. These can be defined into distinct diseases, as serous (75%), endometrioid (10%), clear-cell (5–10%), and mucinous (5–10%) ovarian cancers, which are usually grouped into low-grade or high-grade tumors (Guarneri et al., 2011). Nowadays, it is widely accepted that serous, mucinous, endometrioid, clear cell, and other histotypes

TABLE 6 | Expression of STS and SULTs in endometrial cancer.

| Gene | Level | Regulation | References |
|---|-------------------------|--|-------------------------|
| STS | mRNA | ≈ Cancer/adjacent tissue; EC type 1 | Smuc and Rizner, 2009 |
| | | ↑ Cancer/adjacent tissue; EC type 1 (74%) and type 2 (26%) | Lépine et al., 2010 |
| | Protein | 86% EC | Utsunomiya et al., 2004 |
| | | 82% Cancer weak to moderate/normal endometrium weak (glandular cells) | Human Protein Atlas |
| Activity (E1-S) | ↑ EC/normal endometrium | Adessi et al., 1984; Prost et al., 1984; Naitoh et al., 1989; Urabe et al., 1989 | |
| | ↓ EC/normal endometrium | Tanaka et al., 2003 | |
| DHEA-S | | ↑ EC/normal endometrium | Abulafia et al., 2009 |
| SULT1E1 | mRNA | ≈ Cancer/adjacent tissue; EC type 1 | Hevir et al., 2011 |
| | | Borderline ↑ Cancer/adjacent tissue; EC type 1 (74%) and type 2 (26%) | Lépine et al., 2010 |
| | Protein | 22% EC | Utsunomiya et al., 2004 |
| ↑ EC/adjacent endometrium Not detected in cancer | | Xu et al., 2012 Human Protein Atlas | |
| SULT2B1 | mRNA | ↑ Cancer/adjacent tissue; EC type 1 | Hevir et al., 2011 |
| | Protein | Moderate staining in cancer | Human Protein Atlas |

EC, endometrial cancer.

of ovarian cancers represent molecularly and etiologically distinct diseases (Vaughan et al., 2011). The etiology of ovarian cancer can be explained by the “incessant ovulation theory” and the “gonadotropin theory” (Stadel, 1975; Fathalla, 2013). An increasing body of data suggests that ovarian cancer is estrogen dependent, although the role of estrogens in this disease has not yet been investigated thoroughly (Chura et al., 2009). Genetic susceptibility studies have associated SNPs in the *ESR2* gene that codes for ERβ with significantly increased risk of ovarian cancer (Lurie et al., 2011), and epidemiological studies (Women’s Health Initiative and Million Women Studies: (Anderson et al., 2003; Beral et al., 2007) have also suggested that both estrogen only and estrogen–progesterone hormone replacement therapies increase the risk of ovarian cancer (Modugno et al., 2012). However, the current lack of knowledge warrants further studies on the mechanisms of steroid hormone actions in ovarian cancer, followed by clinical trials that may also target estrogen actions.

The expression of STS has been studied at the mRNA and protein levels (Table 7). No significant differences were reported between epithelial ovarian carcinoma and ovarian surface epithelia tissue and primary cell cultures at the mRNA and protein levels (Ren et al., 2015). However, Okuda et al. detected STS staining in 70% of ovarian clear-cell adenocarcinoma, 33% of serous adenocarcinoma and 50% of mucinous adenocarcinoma, thus suggesting the importance of STS in this pathophysiology (Okuda et al., 2001). In contrast to these data, the Human Protein Atlas reports low to medium expression of STS in only two samples of mucinous adenocarcinoma out of 12 serous, mucinous and endometrioid ovarian cancer samples (Uhlén et al., 2015). The STS activity has been studied by two groups: Ren et al. reported higher activity in the SKOV-3 and PEO epithelial ovarian carcinoma cell lines vs. the OSE normal ovarian surface epithelium cell line (Ren et al., 2015), and Chura et al.

reported correlations between increased STS activity and lower progression-free survival of patients (Chura et al., 2009).

The expression of the *SULT1E1* gene has only been investigated by one group (Ren et al., 2015; Table 7). They reported that *SULT1E1* expression was down-regulated in epithelial ovarian carcinoma vs. the OSE normal ovarian surface epithelium cell line, and also that SULT activity was lower in SKOV-3 and PEO cells vs. OSE cells. This all supports the importance of local estrogen formation via the STS pathway (Ren et al., 2015). Using three different anti-SULT1E1 antibodies, SULT1E1 was detected in two of 12 cores of ovarian cancer, with low to high staining observed mainly in mucinous ovarian cancer (Uhlén et al., 2015). With two polyclonal anti-SULT2A1 antibodies, SULT2A1 was detected in two to six of 12 cores, with low to medium intensity, while with three different anti-SULT2B1 antibodies, medium to high intensity staining was reported for SULT2B1 in seven to 12 of 12 tissue microarray cores (Uhlén et al., 2015). To date, there have been no other reports on the expression of SULT2A1 and SULT2B1 in ovarian cancer. Based on these data, DHEA-S cannot be excluded as a potential precursor molecule for local estrogen formation in ovarian cancer.

SULFATASE AS A TARGET FOR TREATMENT OF GYNECOLOGICAL DISEASE

There is a plethora of data that supports the important role of STS in individual gynecological diseases, with disturbances reported for the balance between the STS and SULT enzymes. Although the observed STS mRNA and protein levels were rarely increased, higher STS activities have been seen in the majority of

TABLE 7 | Expression of STS and SULTs in ovarian cancer.

| Gene | Level | Regulation | References |
|---------|-----------------|--|---|
| STS | mRNA | ≈ EOC/OSE | Ren et al., 2015 |
| | Protein | Expressed EOC and OSE 70% OCCA; 33% serous and 50% mucinous adenocarcinoma 17% Cancer low/moderateNormal ovary low (stromal cells) | Ren et al., 2015 Okuda et al., 2001 Human Protein Atlas |
| | Activity (E1-S) | ↑SKOV-3, PEO-1 vs. OSE ↑STS ↓progression-free survival | Ren et al., 2015 Chura et al., 2009 |
| SULT1E1 | mRNA | ↓EOC/OSE | Ren et al., 2015 |
| | Protein | Expressed EOC and OSE 17% Cancer moderate/normal ND | Ren et al., 2015 Human Protein Atlas |
| | Activity (E1) | ↓SKOV-3, PEO-1 vs. OSE | Ren et al., 2015 |
| SULT2A1 | Protein | 17%-50% Cancer low/moderateNormal ovary/ND | Human Protein Atlas |
| SULT2B1 | Protein | 58%-100% Cancer moderateNormal ovary/weak | Human Protein Atlas |

EOC, epithelial ovarian carcinoma; OSE, ovarian surface epithelia; OCCA, ovarian clear-cell adenocarcinoma.

pathological tissues and in model cell lines, including cancerous endometrium (Adessi et al., 1984; Prost et al., 1984; Naitoh et al., 1989; Urabe et al., 1989; Day et al., 2009), ovarian cancer cell lines (Day et al., 2009; Ren et al., 2015), and adenomyosis (Yamamoto et al., 1993; Ezaki et al., 2001). This is in line with the higher catalytic efficiency of STS vs. SULT (Table 1), and in some cases, higher expression levels of STS (Tables 3, 6). Furthermore, in endometriosis, endometrial cancer, and ovarian cancer, the STS pathway has been shown to prevail over the aromatase pathway (Purohit et al., 2008; Fournier and Poirier, 2009; Hevir-Kene and Rižner, 2015; Ren et al., 2015), which substantiate the potential of STS as a drug target.

Lack of correlation between STS mRNA levels and STS activity imply that post-translational modifications might increase STS activity. Additionally, increased uptake and decreased excretion of the sulfated steroids might also be recognized as enhanced STS activity, which would explain why RNA levels are less informative (Newman et al., 2000). As not much is known about the transport of E1-S and DHEA-S across the plasma membrane in these diseased tissues, their uptake and excretion should be studied, as this will help us to better understand local estrogen formation and actions.

SULFATASE INHIBITORS AND CLINICAL TRIALS

The development of STS inhibitors started in the 1990s, and to date, this has led to two compounds that have entered clinical trials (Poirier, 2015). STS inhibitors have been developed by several research groups and several pharmaceutical companies, and the current status of this field has been a topic of several educative reviews in the last few years (Mostafa and Taylor, 2013; Sadozai, 2013; Thomas and Potter, 2013, 2015; Williams, 2013; Poirier, 2015). In general, the large number of STS inhibitors known to date can be divided into steroidal

and nonsteroidal compounds, and further into sulfomoylated and nonsulfomoylated compounds (Maltais and Poirier, 2011). Among the steroidal compounds, estrogen O-sulfamates have been the most intensively studied in *in-vitro* and *in-vivo* models. These have included E1-3-O-sulfamate (EMATE) and E2-3-O-sulfamate (E2MATE), where EMATE was identified as the first irreversible STS inhibitor, although it was originally developed as a prodrug for estrogen replacement therapy (Sadozai, 2013; Thomas and Potter, 2015).

Nonsteroidal inhibitors have also been developed, and an irreversible STS inhibitor, 667 Coumate (also known as STX64 and BN83495, and more recently referred to as irosustat), shows higher potency than EMATE (IC₅₀, 8 nM vs. 25 nM, at 20 μM E1-S, against STS from placental microsomes) (Woo et al., 2000). This compound has high bioavailability, which was explained by its sequestration within erythrocytes, where it binds to carbonic anhydrase II (IC₅₀, 25 nM) (Ho et al., 2003). A plethora of EMATE and 667 Coumate derivatives have been developed in the last few years as 2nd and 3rd generation STS inhibitors (Sadozai, 2013; Thomas and Potter, 2015). These have included the steroidal compound KW-2581 that showed no estrogenic activity (Ishida et al., 2007), and STX213 and STX1938, which have shown greater potency than 667 Coumate (Foster et al., 2008b).

In addition to classical STS inhibitors, dual inhibitors that target STS and aromatase have also been developed (Sadozai, 2013), as well as compounds with dual actions as STS inhibitors and prodrugs of selective estrogen modulators (Sadozai, 2013). Here, the nonsteroidal dual aromatase–STS inhibitor STX681 has shown great potential for treatment of hormone-dependent breast cancer (Foster et al., 2008a), and the dual sulfamate STS inhibitor and antiestrogen SR16157 has also been studied (Rasmussen et al., 2007; Sadozai, 2013).

The published data imply that inhibitors of STS have the potential for treatment of individual gynecological diseases. In the case of endometriosis, STS activity correlates with the

severity of this disease, and Purohit et al. reported that the STS inhibitor STX64 almost completely blocked STS activity *in vitro* in eutopic and ectopic tissue from patients with peritoneal endometriosis (Purohit et al., 2008). Furthermore, E2MATE inhibited STS activity in endometrial tissue *in vitro* and *in vivo* in animal models, including in mouse uterus, liver, leukocytes and endometriotic lesions (Colette et al., 2011). Also, the inhibitor STX64 has been investigated in intact mouse endometrial cancer xenografts and ovariectomized mouse endometrial cancer xenograft models, and in the latter case, STX64 showed significant inhibition after daily 1–10 mg/kg oral doses (Foster et al., 2008c), thus demonstrating the great potential of STS inhibitors as novel anticancer drugs. To the best of our knowledge, STS inhibitors have not yet been investigated in ovarian cancer, adenomyosis and myoma uteri, neither *in vitro* nor *in vivo*.

Several clinical studies have already been performed with STS inhibitors (Thomas and Potter, 2015). Irosustat (i.e., 667 Coumate) was the first STS inhibitor to enter phase I clinical trials, in post-menopausal women with ER-positive breast cancer (NCT01840488); (Stanway et al., 2006). Later, two phase II clinical studies were reported in breast cancer patients (ClinicalTrials.gov): the IPET trial was designed to look at the effects of irosustat using positron emission tomography scanning (Thomas and Potter, 2015), while the IRIS trial investigated the effects of combined treatment with irosustat and anastrozole (an aromatase inhibitor) (NCT01785992). Unfortunately no study data are publicly available for these trials.

Irosustat has also been investigated in ER-positive advanced/recurrent endometrial cancer in a phase II study (NCT00910091). In this study, irosustat was evaluated vs. progestin megestrol acetate in 73 patients, with median age 68 years (range, 37–85 years). Here, 36 patients were randomized to irosustat (40 mg/day), and 37 to megestrol acetate (160 mg/day) (Pautier et al., 2012). After 6 months of treatment, 36.1 and 56.8% of the patients treated with irosustat and megestrol acetate, respectively, were alive and without disease progression. Progression free survival was 16 and 32 weeks for irosustat and megestrol acetate, respectively. Thus, in patients with advanced and recurrent disease, irosustat showed much lower clinical benefit compared to progestin megestrol acetate, which questioned the suitability of STS inhibitors for treatment of endometrial cancer.

In a murine model, E2MATE reduced the weight of the endometriotic lesions, but had no effects on proliferation and apoptosis, or on STS expression (Colette et al., 2011), which led the Swiss-based biopharmaceutical company PregLem to investigate E2MATE in endometriosis patients. As described by Pohl et al. they first examined the effects of E2MATE in a

phase I study (SAPHIR; EudraCT number: 2007-005662-12) in healthy women of reproductive age, through which they showed that E2MATE can inhibit STS in peripheral blood mononuclear cells, although it failed to inhibit STS in eutopic endometrium (Pohl et al., 2014). As a continuation, they investigated the effects of E2MATE (4 mg/week) and/or norethindrone acetate (NETA; 10 mg/day) in healthy nonpregnant women of reproductive age (i.e., 24–39 years). Twenty-four women were randomized to E2MATE, NETA or the combination E2MATE+NETA, for 4 weeks of treatment and 12 weeks of follow-up. In both the E2MATE and E2MATE+NETA groups, the STS activity in peripheral blood mononuclear cells and in the endometrium decreased by 90–91% and 89–96%, respectively, during treatment, and these inhibition levels remained high also 1 month after the treatments (Pohl et al., 2014). E2MATE and NETA have been further studied in endometriosis patients in a phase II study (EudraCT Number: 2011-005167-24), although at present, no results are publicly available.

CONCLUSIONS AND PERSPECTIVES

The STS pathway is clearly implicated in local estrogen formation, and is thus also associated with enhanced estrogen actions. A vast amount of data supports an important role for STS in hormone-dependent diseases, including gynecological diseases like endometrial cancer, ovarian cancer, endometriosis, and adenomyosis, and indirectly also in uterine fibroids. However, the clinical studies that have evaluated STS inhibitors in gynecological diseases to date have not provided convincing data. Although the dual STS and aromatase inhibitors and dual action inhibitors/antiestrogens might provide better clinical performances compared to the classical STS inhibitors, these agents have not reached clinical studies to date. As the intricate local estrogen formation also depends on membrane transport of the sulfated steroids, this aspect needs to be investigated more in detail. This knowledge might contribute to a logical interpretation of the clinical studies to date, and might lead to the identification of novel drug targets and combined treatments that will target individual transporters and the STS enzyme.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and approved it for publication.

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Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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